UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE

IN RE: VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION **This Document Relates to All Actions**	MDL No. 2875 Honorable Robert B. Kugler, District Court Judge Oral Argument Requested

DEFENDANTS' MEMORANDUM OF LAW IN OPPOSITION TO PLAINTIFFS' MOTION TO PRECLUDE OPINIONS OF DEFENSE EXPERT JON P. FRYZEK, MPH, PH.D.

TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page(s)

Cases

Rules

Pursuant to Federal Rules of Evidence 104, 403, and 702, Defendants' Executive Committee, on behalf of all Defendants in this litigation, submit this Memorandum of Law in Opposition to Plaintiffs' Motion to Preclude Opinions of Defense Expert Jon P. Fryzek, MPH, Ph.D. ("Motion" or "Mot.").[1]

INTRODUCTION

Instead of legal arguments, Plaintiffs focus on a recitation of half-truths and misleading statements in an attempt to paint a picture of Dr. Jon P. Fryzek and his opinions that is entirely unsupported by the actual record. Plaintiffs attempt to attack Dr. Fryzek's credibility, instead of focusing on the standards of Rule 702 of the Federal Rules of Evidence and the pertinent *Daubert* principles. A review of Dr. Fryzek's report and opinions reveals that his opinions more than satisfy the applicable *Daubert* standards.

As demonstrated herein, in reaching his conclusion, Dr. Fryzek applied a methodology generally accepted among epidemiologists and by the courts. He based his literature search and weighing of the evidence on sound, scientific reasoning in accordance with industry standards. Further, Dr. Fryzek's opinion that exposure to NDMA or NDEA is not associated with an increased risk of any of the cancers alleged by Plaintiffs fits the facts of the case and will assist the trier of fact in

[1] The complete Expert Report of Jon. P. Fryzek, MPH, Ph.D., dated August 1, 2021 ("Rep.") is attached as Ex. A with all appendices. Plaintiffs attached an incomplete version to their Motion (Dkt. 1713-2) as Exhibit A (Dkt. 1713-3).

evaluating the general causation question before them. Any purported issues with Dr. Fryzek's credibility or any alleged weaknesses in Dr. Fryzek's opinions as argued by Plaintiffs should be the possible focus of cross-examination at trial—and are certainly not grounds for the exclusion of his opinions and testimony.

Because Dr. Fryzek is qualified to offer these opinions that are premised on reliable scientific principles and fit the facts of the case, Defendants respectfully request that Plaintiffs' Motion be denied in its entirety.

FACTUAL AND PROCEDURAL BACKGROUND

I. SUMMARY OF DR. FRYZEK'S OPINIONS.

Dr. Fryzek rendered the following opinions in his report:

> Opinion 1: The scientific evidence does not support an increased risk of cancer from the low levels of N-Nitrosodimethylamine (NDMA) or N-nitrosodiethylamine (NDEA) with the use of valsartan products.
>
> Opinion 2: The scientific evidence does not support an association between dietary intake of NDMA or NDEA and the risk of cancer.

Rep. at 1.

In reaching Opinion 1, Dr. Fryzek determined that "[v]alsartan and valsartan-containing prescriptions are NOT associated with cancer" based on "five articles [that] described the risk of cancer with use of NDMA-containing medications." *Id.* at 13. In reaching Opinion 2, Dr. Fryzek determined that "[c]ancer is not consistently and reliably associated with NDMA or NDEA through diet in the medical literature."

Id. at 18. More specifically, Dr. Fryzek concluded that "[c]ohort studies have not demonstrated that NDMA or NDEA in the diet are associated with any cancer type" based on "six large prospective cohort studies [that] reported data on the risk of cancer with exposure to NDMA, and none [that] reported the risk of cancer with NDEA." *Id.* at 21. Further, in reaching Opinion 2, Dr. Fryzek concluded that "[c]ase-control studies as a whole have not found strong evidence that NDMA or NDEA are associated with cancer" based on "14 case-control studies [that] reported data on the risk of various cancers with exposure to NDMA, including one study that also reported the risk of cancer with NDEA." *Id.* at 24.

II. IT IS UNDISPUTED THAT DR. FRYZEK IS QUALIFIED TO OFFER HIS OPINIONS ON EPIDEMIOLOGY.

Plaintiffs do not dispute that Dr. Fryzek is an expert in the field of epidemiology. *See* Rep. at 1-2. Dr. Fryzek's academic pedigree speaks for itself. He received an undergraduate degree in Biology from Creighton University in 1985, a Master's degree in Public Health from University of Michigan in 1991, and a Ph.D. in Epidemiologic Science from the University of Michigan in 1996. *See id.* at 2.[2] Since receiving his Ph.D. in 1996, Dr. Fryzek has been a practicing epidemiologist. *Id.*

[2] Dr. Fryzek's CV was updated after his report was served (with his CV as Appendix A), and the updated CV was produced to Plaintiffs in advance of Dr. Fryzek's deposition. Plaintiffs filed Dr. Fryzek's updated CV as Exhibit G. *See* Dkt. 1713-9.

Over the course of his long career, Dr. Fryzek has performed and published hundreds of publications in the realm of epidemiology, pharmacoepidemiology, and statistical methods. *See* Rep. at 3. In addition, Dr. Fryzek has taught courses and lectured at several universities on general epidemiology, pharmacoepidemiology, and statistical methods, including the calculation and interpretation of odds ratios, risk ratios, p-values, and meta-analysis summary results to assess signal detection and causality. *See id.* at 3; *see infra* at III.A.1 for discussion of statistical methods.

Dr. Fryzek is well respected in the epidemiological community. He has been elected a member of the American College of Epidemiology and is a member of the International Society of Pharmacoepidemiology. Rep. at 2. Notably, Dr. Fryzek serves as a peer-reviewer of scientific papers for 17 professional journals. *Id.*

III. DR. FRYZEK EMPLOYED A GENERALLY ACCEPTED, RELIABLE METHODOLOGY IN REACHING HIS CONCLUSIONS.

As explained further below, Dr. Fryzek utilized a reliable methodology employed by other epidemiologists in conducting a systematic literature review of existing epidemiological evidence, and then evaluated whether a causal association existed between NDMA or NDEA and cancer by applying the Bradford Hill criteria.

A. Epidemiological Methods For Assessing Whether An Association Exists Between Exposure To An Agent And Disease.

Epidemiology examines whether an agent is capable of causing disease in humans. Reference Manual on Scientific Evidence, at 551-52 (3d Ed. 2011) ("Ref.

Manual").[3] Specifically, "[e]pidemiology assumes that disease is not distributed randomly in a group of individuals and that identifiable subgroups, including those exposed to certain agents, are at increased risk of contracting particular diseases." *Id.* at 551.[4]

Epidemiologists conduct this analysis by reviewing available scientific evidence on a particular research question. Epidemiologists give more weight to evidence that is superior on the hierarchy of evidence to assess whether an association exists. *See In re Neurontin Mktg. & Sales Pracs. Litig.*, 2010 WL 559108, at *1 (D. Mass. Feb. 12, 2010) ("Experts must accord appropriate weights to different levels of evidence, i.e. a randomized, controlled trial, as the 'gold standard' of evidence, must be accorded greater weight than observational, non-controlled studies or case reports."); *In re Johnson & Johnson Talcum Powder Prod. Mktg., Sales Pracs. & Prod. Litig.*, 509 F. Supp. 3d 116, 194 (D.N.J. 2020).

While randomized clinical trials are the gold standard in epidemiology, researchers do not conduct randomized clinical trials on humans where an agent's effects may be harmful. *See* Ref. Manual at 555. Instead, analytical, observational studies of certain populations must be used. *See id.* at 555-56. The two main types

[3] *Available at* https://www.fjc.gov/sites/default/files/2015/SciMan3D01.pdf.

[4] Thus, "[e]pidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?) rather than that of specific causation (i.e., did it cause disease in a particular individual?)." Ref. Manual at 552.

of observational studies are cohort studies and case-control studies, both which observe individuals who have been exposed to an agent and then compare them with individuals who have *not* been exposed. *Id.* at 556-57.

Cohort studies begin with exposed and unexposed people who have not yet developed the studied disease outcome. Then, defined populations are observed over time in order to compare their disease outcomes based on their exposure to the agent. Ref. Manual at 557. Prospective cohort studies collect information about participants in the present (prior to the disease outcome) and then follow the participants forward in time. *Id.* Retrospective cohort studies rely on participants' memories and require them to recall past risk factors, which introduces potential bias into the study. *Id.* Accordingly, prospective cohort studies become the standard for supporting a causal relationship where clinical trials are unavailable. *See id.* at 558.

Case-control studies rank lower than cohort studies on the hierarchy. *See Knight v. Kirby Inland Marine Inc.*, 482 F.3d 347, 352 (5th Cir. 2007) (finding "[c]ase-control studies are not per se inadmissible evidence on general causation" but excluding three case-controls studies as unreliable). They are inherently retrospective given they begin with individuals who have already developed a certain disease, and then those individuals with the disease (cases) are compared with a group of individuals who do not have the disease (controls) in order to

determine the differences in risk factors between the groups. *See* Ref. Manual at 557, 559.

1. Epidemiologists First Assess Whether An Association Exists.

Based on the available studies, "the first question an epidemiologist addresses is whether an association exists between exposure to the agent and disease." Ref. Manual at 566. Exposure to an agent and a disease are associated (or an association exists) when the exposure and disease "occur together more frequently than one would expect by chance." *Id.*

The results of observational studies are reported using metrics known as relative risks ("RR") or odds ratios ("OR"), each of which examines "the degree to which the risk of disease increases when individuals are exposed to an agent." *Id.* RR/OR of exactly 1.0 means the risk in exposed individuals is the same as unexposed individuals, and there is no association between the agent and the disease—*i.e.*, the disease outcome occurred by chance and not the agent exposure. *See* Ref. Manual at 567. RR/OR greater than 1.0 means the risk in exposed individuals is greater than the risk in unexposed individuals. *Id.* To support an inference of causation, courts generally require that the exposure to the agent more than doubled the risk of the studied disease—*i.e.*, the RR or OR is at least 2.0. *See In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1225-26 (D. Colo. 1998) ("Plaintiffs must present expert

testimony demonstrating that exposure to breast implants more than doubled the risk of their alleged injuries.").

Because observational studies necessarily employ imperfect sampling, it is possible to observe an association greater than 1.0 where no true association actually exists. *See* Ref. Manual at 572. Thus, "[b]efore any inferences about causation can be drawn from a study, the possibility of . . . chance [or random error], bias, and confounding" should be examined by epidemiologists. *Id.* at 572-73.

- ***First***, epidemiologists assess random error by analyzing whether a study's results are statistically significant according to confidence intervals.[5] *See* Ref. Manual at 572-57. A confidence interval provides a range (interval) within which the risk likely would fall if the study were repeated numerous times. *Id.* at 573.[6] A result is not statistically significant if range includes 1.0 (*e.g.*, 95% CI: 0.8-3.6) because the results could be due to chance alone. *See id.* at 621.

- ***Second***, epidemiologists assess bias through review of the study design, including analysis of subjects selection and data collection. Ref. Manual at 583-91. For example, research has shown that individuals with a disease tend to recall past exposures more readily than individuals who have not developed the disease, which can distort the results of the study.[7]

- ***Third***, epidemiologists must assess confounding, which occurs when a second agent – the confounder – is associated with the exposure and independently affects the risk of developing the disease. Ref. Manual at 573-74, 591. For example, a study might find that people with gray hair (the studied agent) have

[5] P-values are another statistical method for assessing chance but are not discussed in Motion or herein. *See* Ref. Manual at 250.

[6] A 95% confidence interval, which is the most popular, represents a range in which the RR/OR from repeated samples would fall within the interval 95 times out of 100. *See* Ref. Manual at 245-55, 247, 381.

[7] Another example of bias occurs when using food frequency questionnaires to determine exposure to dietary NDMA or NDEA because participants often over or underestimate the intake of certain foods to make their diets appear healthier.

> a higher rate of death than those with brown hair; however, the true reason for the higher rate of death among the gray haired people is old age (the confounder). *Id.* at 591.

In order to answer the predicate question of whether an association exists, epidemiologists conduct a "formal, transparent, and reproducible search for studies that address [the] proposed research question[,]" otherwise known as a literature review. *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig.*, 174 F. Supp. 3d 911, 929 (D.S.C. 2016) (citation omitted). The goal of the literature review is "to obtain a neutral 'snapshot' of the existing research on a particular question . . . rather than cherry-picking articles based on the [epidemiologists]' biases." *Id.* (citation omitted).

Once an epidemiologist has identified the universe of relevant articles, the strengths and weaknesses of each of those articles must be analyzed to assess whether an association between exposure to an agent and a disease actually exists in the totality of the articles. *See* Ref. Manual at 595; *Johnson & Johnson*, 509 F. Supp. 3d at 164.

2. Epidemiologists Apply The Bradford Hill Criteria To Determine If An Association Is Causal.

Because observational studies are designed to identify statistical relationships between the incidences of disease in one group compared to another group, they do not on their own demonstrate a causal relationship. *See* Ref. Manual at 598. "***Causation is a judgment for epidemiologists***[.]" *Id.* (emphasis added).

If the totality of the available evidence indicates an association exists between the exposure and the disease, epidemiologists then use the Bradford Hill criteria to determine whether a true cause-effect relationship may properly be inferred from the association. *See In re Mirena Ius Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 341 F. Supp. 3d 213, 242 (S.D.N.Y. 2018), *aff'd sub nom. In re Mirena IUS Levonorgestrel-Related Prod. Liab. Litig. (No. II)*, 982 F.3d 113 (2d Cir. 2020) (explaining Bradford Hill criteria "distinguish a causal connection from a mere association"). The Bradford Hill criteria include:

- **Strength**: How strong is the association between the suspected risk factor and the observed outcome;
- **Consistency**: Does the association hold in different settings and among different groups;
- **Specificity**: How closely are the specific exposure factor and the specific health outcome associated, i.e., how unique is the quality or quantity of the response;
- **Temporality**: Does the hypothesized cause precede the effect;
- **Biological plausibility**: Does the apparent association make sense biologically;
- **Coherence**: Is the association consistent with what is known of the natural history and biology of the disease;
- **Experimental verification**: Does any experimental evidence support the hypothesis of an association;
- **Biological analogy**: Are there examples of similar risk factors and similar outcomes; and
- **Dose-response relationship**: Has a dose-response relationship been established, i.e., does the magnitude of the response increase as the magnitude of the dose increases.[8]

[8] While dose-response relationship has a bearing on whether an inference of causation is justified by epidemiologists as a Bradford Hill factor, the relationship between dose and response is actually a hallmark of ***toxicology***. *See* Ref. Manual at

See Ref. Manual at 599-600.

B. Dr. Fryzek's Methodology.

Dr. Fryzek conducted a reproducible, systematic literature review based on the methods outlined above and described in detail in his report. *See* Rep. at 9-11 (describing search terms, databases, inclusion and exclusion criteria); *id.* at 12 (reflecting PRISMA[9] diagram of literature review results). Dr. Fryzek also explained his literature review during his deposition. *See* Tr.[10] at 99:3-7, 115:11-12, 117:3-18, 120:6-121:24.

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603 n.160, 161. For more information on the concept the "dose makes the poison" and the dose-response relationship with regard to the toxicity of drugs, please refer to Pages 10-11 of Defendants' Memorandum of Law in Opposition to Plaintiffs' Motion to Preclude Opinions of Janice K. Britt, Ph.D. Notably, analysis of a dose-response relationship as part of the Bradford Hill criteria "is ***analytically distinct*** from determining whether evidence of the dose to which a plaintiff was exposed is required in order to establish specific causation." Ref. Manual at 603 n.161 (emphasis added).

[9] PRISMA stands for "Preferred Reporting Items of Systematic Reviews and Meta-Analyses," which are best practices for conducting a literature review. *See* Page, et al., *The PRISMA 2020 statement: an updated guidelines for reporting systematic reviews*, BMJ 372 (Mar. 29, 2021), *available at* https://www.bmj.com/content/372/bmj.n71. Dr. Fryzek cited and followed the PRISMA guidelines published in 2009 in conducting his literature search on January 25, 2021—which occurred prior to the publication of the updated PRISMA guidelines in March 2021. However, the only changes to the PRISMA guidelines that are relevant to Dr. Fryzek's review included updating the PRISMA diagram and adding a formal risk of bias assessment. Notably, Dr. Fryzek preformed both of these tasks as part of his January 2021 review; therefore, the updated PRISMA guidelines do not impact Dr. Fryzek's findings.

[10] Dr. Fryzek's deposition transcript (with Errata) ("Tr.") is attached as Ex. B.

Specifically, Dr. Fryzek reviewed and analyzed the totality of the evidence available, including the title and abstract of 1,884 articles and the full text of 117 articles. *See* Rep. at 10.[11] Applying his inclusion and exclusion criteria, Dr. Fryzek isolated 25 studies and assessed all aspects of those studies, including evaluating chance, bias, and confounding for each study. *See* Tr. at 240:16-23; Rep. at 10-11, 15-18, 19-35. After reviewing the totality of the evidence and not finding an association between NDMA/NDEA and cancer, Dr. Fryzek reliably applied the Bradford Hill criteria to further demonstrate that no causal association exists. *See* Rep. at 39-45.

LEGAL STANDARDS

Federal Rule of Evidence 702 governs the admission of expert testimony. *See* Fed. R. Evid. 702. The Third Circuit has clarified that Rule 702 "embodies a trilogy of restrictions on expert testimony: qualification, reliability, and fit." *Ruggiero v. Yamaha Motor Corp., U.S.A.*, 778 F. App'x 88, 93 (3d Cir. 2019) (citing *Schneider ex rel. Estate of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003)).

As a threshold matter, an expert must be qualified to testify about the subjects on which the expert is offered, which requires "specialized knowledge" regarding the area of his/her testimony. *See Ruggiero*, 778 F. App'x at 92-93.

[11] *See also* Tr. at 111:24-112:14, 113:2-113:11, 114:9-115:3, 234:18-236:15, 254:4-16, 270:8-271:4, 272:14-22.

To be reliable, scientific expert testimony must be based on "scientific knowledge." *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 589, 589-90 (1993). Multiple factors should be considered in making this determination, including: "(1) whether the expert's theory or method is generally accepted in the scientific community; (2) whether the expert's methodology can be or has been tested; (3) the known or potential error rate of the technique; [ ] (4) whether the method has been subjected to peer review and publication" and (5) "whether the expert's testimony springs from research independent of the litigation." *In re Viagra (Sildenafil Citrate) & Cialis (Tadalafil) Prod. Liab. Litig.*, 424 F. Supp. 3d 781, 789-90 (N.D. Cal. 2020) (citing *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1316 (9th Cir. 1995)). That said, "[s]o long as an opinion is premised on reliable scientific principles, it should not be excluded by the trial judge; instead the weaknesses in an unpersuasive expert opinion can be exposed at trial, through cross-examination or testimony by opposing experts." *In re Roundup Prod. Liab. Litig.*, 390 F. Supp. 3d 1102, 1109 (N.D. Cal. 2018) (emphasis added)).

The third prong of admissibility, fit, concerns whether the expert's testimony will help the trier of fact resolve disputed factual issues or understand the evidence. *See Schneider ex rel. Est. of Schneider v. Fried*, 320 F.3d 396, 404 (3d Cir. 2003) ("In other words, the expert's testimony must be relevant for the purposes of the case

and must assist the trier of fact."); *In re Diet Drugs Prod. Liab. Litig.*, 706 F. 3d 217, n.7 (3d Cir. (2013).

Importantly, at this stage of the litigation, the relevant question "is not whether [Dr. Fryzek] [is] right. The question is whether [Dr. Fryzek] [has] offered opinions that would be admissible at a jury trial." *Roundup,* 390 F. Supp. 3d at 1108-09.

ARGUMENT

I. DR. FRYZEK'S METHODOLOGY SATISFIES THE STANDARDS UNDER RULE 702.

Plaintiffs' strained efforts to preclude Dr. Fryzek's opinions based on a purportedly "unreliable" method are baseless. As set forth below, each of Plaintiffs' arguments fails to refute the fact that Dr. Fryzek's methodology clearly satisfies the standard under Rule 702.

A. Dr. Fryzek Followed A Standard Methodology.

As Plaintiffs acknowledge, Dr. Fryzek employed the standard method for the literature review in his report that he and other epidemiologists use for peer reviewed, published review articles. *See* Mot. at 22 ("In deposition, Dr. Fryzek testified that he employed his typical methodology when coming to his opinions in this litigation.").[12]

[12] *See also* Tr. at 117:3-117:24 ("I just want to be clear, that this is – this is very typical of how you do a PRISMA methodology to look at the narrative review. . . . This is – this is just following the PRISMA guidelines. This graph even comes from the PRISMA website. . . . So we do this for any type of review, even review articles we publish. . . . It's the standard methodology to do a literature review.").

While Dr. Fryzek has not submitted his report in this litigation for peer review or publication,[13] the fact that he used the standard methodology for a literature review in his field—the same method he would use for authoring review articles that are then peer reviewed and published—only underscores the reliability of his methodology here. Indeed, one factor demonstrating the reliability of an expert opinion is whether the ***method*** utilized by an expert in forming his opinion – and not the opinion itself – has been subjected to peer review and publication. *See supra* at 13; *Viagra & Cialis*, 424 F. Supp. 3d at 791 (citing *Daubert*, 43 F.3d at 1316).

Further, Plaintiffs' argument that the reliability of Dr. Fryzek's opinions is somehow lessened because he formed them "solely for the purposes of litigation, and did not adequately educate himself on NDMA prior to forming his opinions[,]" this is unsupported by the law. *See* Mot. at 25. The two cases Plaintiffs cite in support of this contention indicate that "whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the litigation" is merely ***a factor*** to be considered. *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 594 (D.N.J. 2002); *aff'd,* 68 F. App'x 356 (3d Cir. 2003); *Daubert*, 43 F.3d at 1317.[14] Further, even if Dr. Fryzek's

[13] "[E]xpert testimony may still be reliable and admissible without peer review and publication" of the specific opinions offered in the litigation. *Viagra & Cialis*, 424 F. Supp. 3d at 791.

[14] Indeed, it is without question that an expert reaching opinions only for purposes of litigation does not automatically render an opinion unreliable. *See Viagra &*

research was conducted for the purposes of litigation, he merely needs to demonstrate other indicia of reliability, including "showing that [he] 'followed the scientific method, as it is practiced by (at least) a recognized minority of scientists in their field.'" *Viagra & Cialis*, 424 F. Supp. 3d at 790 (citation omitted).

Unquestionably, Dr. Fryzek followed the scientific method employed by epidemiologists generally. Further, Dr. Fryzek is an epidemiologist with a 26-year career who has published hundreds of peer-reviewed articles studying whether a causal association exists between exposure to an agent and a hypothesized adverse result. The fact that he had not done *prior* specific research on NDMA/NDEA and cancer does not call into question the reliability of Dr. Fryzek's methods—Dr. Fryzek is qualified to have conducted the standard methodology in his industry and to offer his opinions in this litigation flowing from that methodology.

B. Dr. Fryzek Conducted A Reliable, Reproducible, Neutral Literature Review And Followed His Inclusion And Exclusion Criteria.

Each of Plaintiffs' attempts to color the Court's view of Dr. Fryzek's reliable, reproducible, and neutral literature review should be rejected. In general, Plaintiffs claim Dr. Fryzek's literature review is "flawed" because he "did not follow his own

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Cialis, 424 F. Supp. 3d at 791 ("While independent research into the topic at issue is helpful to establish reliability, its absence does not mean the experts' methods were unreliable."); *Daubert*, 43 F.3d at 1317 ("That an expert testifies for money does not necessarily cast doubt on the reliability of his testimony, as few experts appear in court merely as an eleemosynary gesture.").

literature inclusion and exclusion criteria" and therefore he "in essence followed no methodology." Mot. at 10-12, 24-25. Plaintiffs make three arguments in support of this contention. First, Dr. Fryzek "included two studies on ranitidine, which did not meet his exclusion criteria" but "had no justification why he excluded other ranitidine studies"; second, Dr. Fryzek "excluded 14 studies because they were reviews or meta-analyses but still included one meta-analysis in his report"; and third, Dr. Fryzek "excluded human occupational studies that demonstrate an increased risk of cancer due to NDMA exposure, even though those studies would have been identified by his literature search terms, met his inclusion criteria, and did not meet his exclusion criteria." *Id.* at 24-25.

Contrary to Plaintiffs' assertions, Dr. Fryzek adhered to his inclusion and exclusion criteria, which is expressly set forth in his report and was explained again during Dr. Fryzek's deposition. Studies were included if they were observational studies of a group of people exposed to valsartan, NDMA, or NDEA who developed cancer, compared to a group of unexposed or less exposed people. Rep. at 10. Studies were nonetheless excluded if they (1) were not cohort or case-control studies, *i.e.*, case reports or narrative reviews,[15] (2) studied animals or non-human laboratory testing, or (3) were not exposed to the necessary exposure, did not compare those

[15] Dr. Fryzek explains his reasoning for this exclusion criterion at length in his report. *See* Rep. at 5-7.

exposed to those not, or did not study cancer as a disease outcome. Thus, Dr. Fryzek's inclusion and exclusion criteria were correctly applied to isolate observational studies of humans exposed to valsartan, NDMA (and its synonyms),[16] NDEA (and its synonyms) and the disease outcome of cancer.

1. Dr. Fryzek Adhered To His Inclusion And Exclusion Criteria With Regard To Ranitidine Studies.

First, studies analyzing NDMA-containing medications, such as ranitidine, met Dr. Fryzek's inclusion criteria if the study (a) included the term "NDMA" or one of its synonyms and (b) reported cancer outcomes. *See* Rep. at 9-10 (identifying search terms and inclusion and exclusion criteria); *id.* at 13 ¶ 30 ("Of the 25 abstracted studies, five examined the risk of cancer with specific medications that potentially contained NDMA."), 17 ¶ 37, 18 ¶ 39. Studies on ranitidine were excluded if (a) they did not meet Dr. Fryzek's inclusion criteria as outlined in Paragraph 27 of his report or (b) if they met Dr. Fryzek's exclusion criteria as outlined in Paragraph 28 of his report. *Id.* at 10 ¶¶ 27-28. For example, a study analyzing ranitidine that contained NDMA would have nevertheless been excluded

[16] Plaintiffs attempt to mislead the Court when they claim that Dr. Fryzek's literature review could not have isolated the relevant literature because Dr. Fryzek did not recognize *in his deposition* one synonym of NDMA: dimethylnistrosamine. Mot. at 10. Dr. Fryzek's report clearly lists "dimethynitrosamine" as an NDMA synonym that was captured by his literature review. Rep. at 10.

if it did not report any cancer risk outcome. *See id.*[17] Dr. Fryzek reiterated these criteria at his deposition when he explained to Plaintiffs' counsel that the ranitidine studies were found when he "looked at NDMA-containing medication" and that certain other ranitidine studies were not included "[b]ecause they weren't categorized as NDMA-containing medication." Tr. at 121:18-122:5.[18]

Thus, as demonstrated, Dr. Fryzek did not deviate from his literature search inclusion or exclusion criteria in selecting ranitidine studies for analysis in his report. Plaintiffs' contention that Dr. Fryzek has "no justification [for] why he excluded other ranitidine studies" is incorrect. Mot. at 24.

2. Dr. Fryzek Adhered To Common Practice With Regard To Meta-Analyses And Included Discussion Of One Meta-Analysis To Rebut Plaintiffs' Expert's Reliance On It.

Second, Dr. Fryzek employed standard practice with respect to reviews and meta-analyses – which are studies that assess the results of a body of previous

[17] *See, e.g.*, Zeng, et al., *Oral intake of ranitidine increases urinary excretion of N-nitrosodimethylamine*, 37(6) CARCINOGENESIS 625-34 (2016) (article that has since been retracted but arose in literature search and was properly excluded because it did not report cancer risk) (attached as Ex. C).

[18] Further, in response to a question regarding whether Dr. Fryzek had "ever reviewed any other ranitidine NDMA studies besides the two listed in your expert report," Dr. Fryzek answered yes. Tr. at 127:6. Dr. Fryzek clarified that the literature review for his report was completed at the end of January 2021, and he updated the search in August 2021 "to see if any additional or major studies ha[d] been produced since that time." *Id.* Dr. Fryzek testified "the studies of ranitidine didn't show anything striking in terms of relationship with cancer" and thus his conclusions in his report remained unchanged with the updated search. *Id.*

research on a subject to derive conclusions on the trends of that research – by analyzing the individual studies that comprise the meta-analysis on their own. *See* Rep. at 10 ¶ 28-29 (listing "narrative reviews" under exclusion criteria and noting that "14 [articles] were eliminated because they were reviews or meta-analyses" and "[a]n additional eight papers were added from reading relevant reviews"); *id.* at 5-7.

One meta-analysis raised in the Motion, Song et al., Ex. D, was analyzed in Dr. Fryzek's report for two reasons. First, as is proper, all of the individual studies reviewed in Song also met Dr. Fryzek's inclusion criteria (and did not meet his exclusion criteria) and were analyzed individually in his report. *See* Rep. at 28 ¶ 62. Second, Dr. Panigrahy – Plaintiffs' own expert – relied on this same meta-analysis in forming his opinions, and Dr. Fryzek included it in his report to discuss the problems with it and Dr. Panigrahy's reliance on it. *See id.* at 28 ¶ 62, 56 ¶ 141 (noting that Dr. Panigrahy "ignored the high heterogeneity between the studies (I^2=75.8%) reported by Song in the meta-analysis");[19] *In re Mirena IUD Prods. Liab. Litig.*, 169 F. Supp. 3d 396, 418-19 (S.D.N.Y. 2016) (holding "pointing to the . . . weaknesses of studies on which [p]laintiffs rely, and evaluating them in light of their . . . experience, training and research" is "a logical and valid approach").[20]

[19] *See* Dr. Panigrahy's Report, Dkt. 1716-3.

[20] It is also true that experts are permitted to derive rebuttal opinions based solely on their experience and training. *Id.*; *In re Zyprexa Prods. Liab. Litig.*, 489 F. Supp. 2d 230, 285 (E.D.N.Y. 2007) (noting that defense experts "have no burden to produce models or methods of their own; they need only attack those of plaintiffs' experts").

Accordingly, Dr. Fryzek included Song and excluded other meta-analyses for sound scientific reasons.

3. Dr. Fryzek's Exclusion Of Human Occupational Studies Was By Design And In Accordance With The Criteria For His Literature Search.

Third, Plaintiffs misunderstand the criteria for Dr. Fryzek's literature search in alleging that Dr. Fryzek excluded human occupational studies that "would have been identified by his literature search terms, met his inclusion criteria, and did not meet his exclusion criteria." Mot. at 12, 24-25. Contrary to Plaintiffs' contention that Dr. Fryzek "diverged from his stated methodology" (*id.* at 12), Dr. Fryzek excluded human occupational studies in accordance with his criteria.

Specifically, Dr. Fryzek's review sought to find studies examining humans exposed only to valsartan, NDMA or NDEA. *See* Rep. at 9-10. With occupational studies, Dr. Fryzek found no occupational studies examining workers uniquely exposed to NDMA or NDEA. *See id.* at 51 ¶ 124; Tr. at 421:1-422:9. ("[T]he occupational exposure to rubber workers had too many co-exposures, exposures to

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Plaintiffs' take issue with Dr. Fryzek's opinion criticizing Dr. Panigrahy because "[i]f NDMA exposure is a trigger for cancer growth and development," then "cancer incidence would be far higher in the general population and the diet studies would show much stronger effects with the daily exposure humans receive from NDMA." Rep at 53 ¶ 142; Mot. at 20. But this opinion is clearly not *ipse dixit*: it is, first, based on evidence, including that "[t]he studies of NDMA containing prescriptions . . . that had short follow-up time should have seen increased risks of more cancer than just liver cancer if this were true," and, second, properly based on Dr. Fryzek's experience, training, and research. Rep. at 56 ¶ 142.

other things. So it's hard to tease out the NDMA in those workers. So it's not really meaningful."). Therefore, these studies were properly not included in Dr. Fryzek's literature review. Tr. at 421:24-422:1 ("I didn't do a literature search on those [occupational studies]."). Dr. Fryzek further explained his reasoning at his deposition: "[o]ne thing you have to try to understand in epidemiology is how representative your population is to the population you're concerned about. And rubber workers isn't the same as a valsartan user." Tr. at 442:16-21.

Clearly, Dr. Fryzek did not ignore occupational studies. In fact, Dr. Fryzek addressed both human occupational studies relied upon heavily by Plaintiffs (Hidajat, Dkt. 1717-9, and Straif, Dkt. 1717-15) and provided sound scientific reasoning for why these studies do not support Plaintiffs' experts' conclusions of a causal association between NDMA/NDEA and various cancers alleged.[21] Thus, Plaintiffs have not "identified any apparently relevant study that Dr. [Fryzek] should have discussed but omitted completely." *In re Zimmer Nexgen Knee Implant Prod. Liab. Litig.*, 2015 WL 5050214, at *12 (N.D. Ill. Aug. 25, 2015).

In conclusion, Dr. Fryzek adhered to his literature review's inclusion and exclusion criteria, including and excluding studies for objective, scientific reasons. Dr. Fryzek did not cherry-pick studies to support his conclusions but instead

[21] *See* Rep. at 51 ¶ 124, 52 ¶ 127, 52-53 ¶ 129, 54 ¶ 135, 55 ¶ 140 (analyzing issues with Plaintiffs' experts' reliance on Hidajat); *id.* at 52-53 ¶ 129, 53 ¶ 130 (analyzing issues with Plaintiffs' experts' reliance on Straif).

conducted a reproducible literature search that provided an objective snapshot of the existing research on the question at issue in accordance with Rule 702 standards. *See In re Lipitor*, 174 F. Supp. 3d at 929.

C. Dr. Fryzek Individually Assessed Each Study And The Totality Of The Evidence.

As explained in detail below, Dr. Fryzek, contrary to Plaintiffs' assertions, assessed the totality of epidemiological evidence by examining each study's potential for chance, bias, and confounding. Dr. Fryzek then reliably assessed the body of evidence as a whole to determine whether any associations existed between NDMA/NDEA intake and various cancers.

1. Dr. Fryzek Individually Assessed Confounding In Each Study.

The Court should reject Plaintiffs' request that Dr. Fryzek "be precluded from offering opinions regarding confounding factors on any specific study" because he allegedly "only discusses confounders generally in his expert report." Mot. at 5-6, 18. It is true that Dr. Fryzek discusses the different potential confounders for different types of cancers generally in his report. *See* Rep. at 31 ¶¶ 67-80 (listing potential confounders by cancer type); *id.* at 34 ¶ 81 ("I note that very few of the risk factors discussed here for each of the cancers of interest were even considered in the epidemiological studies that I reviewed in this case."). However, contrary to Plaintiffs' statement, Dr. Fryzek also addresses confounders (as well as strengths and weaknesses) on a study-specific basis. *See id.* at 15-35.

Plaintiffs' own Motion actually acknowledges Dr. Fryzek's testimony that "confounding is a very study-specific thing" and "[y]ou have to look within each study." Mot. at 17-18 (quoting Tr. at 375:17-22). Notably, Dr. Fryzek also testified that epidemiologists "have to look at the whole study. We have to look at potential confounders they controlled for, sample size, what it represents, there's a lot of factors besides just the confidence interval to statistical significance of a study that shows causality." Tr. at 240:16-23.

Yet Plaintiffs' Motion then ignores that Dr. Fryzek's report ***does analyze whether each study sufficiently accounted for confounding factors or whether the study's failure to control for confounding limited the use of the study's results***. *See, e.g.*, Rep. at 15 (discussing Gomm, Dkt. 1717-7: "Important liver cancer risk factors were not controlled for as well, including hepatitis B and C infections, nonalcoholic fatty liver disease, cirrhosis, obesity, heavy alcohol use, and others (American Cancer Society, 2019n)."); *id.* at 21, ¶ 45 (discussing Knekt, Dkt. 1717-11: "While the association between NDMA and colorectal cancer observed in this study is plausible, the authors state that confounding cannot be ruled out. The association seen may be due to some unmeasured dietary or life-style habits related to development of the disease.").[22]

[22] *See, e.g.*, Rep. at 27-28 ¶ 60, 24-25 ¶ 53, 23 ¶ 49.

Plaintiffs' suggestion that Dr. Fryzek did not "identify specific studies that failed to account for specific confounders, or the magnitude of impact that the confounder could have potentially had on the specific study" is inaccurate. Mot. at 5, 17-18. Dr. Fryzek reliably accounted for confounding within his analysis of each study and therefore his opinions cannot be considered unreliable.[23]

2. Dr. Fryzek's Analysis Of The Evidence Rests On Good Grounds.

Plaintiffs argue that "the method that yielded [Dr. Fryzek's] opinion in [his] report should be scrutinized closely" because "[a]ll the literature cited by Dr. Fryzek . . . refute the opinions that he is attempting to offer in this litigation." Mot. at 26-27. In their Motion, Plaintiffs list one single RR/OR from within a study cited by Dr. Fryzek that benefits Plaintiffs' position and conclude that every study he cites "demonstrate[s] an increased risk of cancer with increasing NDMA exposure." *Id.* at 12-13. Plaintiffs employed a similar tactic during Dr. Fryzek's deposition, isolating a single statistically significant result from one study and questioning Dr. Fryzek as to how he could possibly draw a conclusion that no association exists.

[23] Plaintiffs' Motion also suggests that Dr. Fryzek previously published studies finding that certain exposures do not increase the risk of cancer, but he points to those same exposures in his report as potential risk factors for cancer. In grasping to connect these dots, Plaintiffs ignore that Dr. Fryzek's studies were published in 2001 and 2011—***a decade ago***. Dr. Fryzek's studies have been and always are based on the evidence available to him at the time in accordance with a standard methodology.

Plaintiffs' own "cherry-picking" of positive results as opposed to evaluating the totality of the evidence is improper. Epidemiologists must base their opinions on an assessment of all available scientific evidence – taking bias, confounding, and statistical significance into account. *See Johnson & Johnson*, 509 F. Supp. 3d at 164.[24] Therefore, Plaintiffs' argument cannot possibly support a determination that Dr. Fryzek's method is unreliable.

For example, Plaintiffs condemn Dr. Fryzek for citing "a single case-control study related to NDMA/NDEA exposure and pancreatic cancer . . . [which] found that plant sources of NDMA were associated with a statistically significant increased risk at high levels of intake compared to the lowest levels" and that "increasing intake of NDEA, however, increased the risk of pancreas cancer at all quartiles of intake compared to the lowest level." Mot. at 17 (quoting Rep. at 31 discussing Zheng, Dkt. 1717-14). Yet, Plaintiffs disregard half of Dr. Fryzek's discussion of this study, as well as the results that ***do not indicate an association***:

> Plant sources of NDMA were associated with a statistically significant increased risk at high levels of intake compared to the lowest level (Q4 OR = 1.93, 95% CI: 1.42-2.61, p-trend <0.0001), ***but animal sources of NDMA had no statistically significant increased risk (Q4 OR = 1.17, 95% CI: 0.89-1.54, p-trend = 0.26)***. . . . ***No statistically significant increased risks were seen with intake of specific foods, including processed meats that have a high NDMA content***.

[24] Space limitations prevent Defendants from explaining all of Plaintiffs' cherry-picking in their Motion, but similar rebuttals can be made in every instance.

Rep. at 31 (emphasis added). Dr. Fryzek also testified about the limitations of the results of this study, informing Plaintiffs that a proper analysis would not just isolate one finding:

> Which you have to be mindful of how they are doing the study. I mean, you're just looking at – again you're just looking at the findings here. I mean they – so they did the study and they only looked at diet in the past year. They didn't look at any changes in the diet. They didn't look at lifetime diet. A lot of questions you have in this type of study. And I explain that at the very beginning [of my report] about the problems with frequency questionnaires in these type of diet studies.

Tr. at 348:22-349:11.

In another example, Plaintiffs contend "[a]ll three case-control NDMA lung cancer studies cited by Dr. Fryzek found varying degrees of increased risk of lung cancer with NDMA exposure, and he failed to exclude the significance of those studies based on any scientific analysis." Mot. at 14. In fact, Dr. Fryzek summarized the results of lung cancer studies and assessed any potential causal connection as a whole, appropriately weighing the epidemiological evidence in accordance with the hierarchy and based on sound scientific reasoning. *See* Rep. at 24-25.[25] More specifically, Dr. Fryzek found that "[w]hile the two case-control studies described above saw a risk between higher levels of NDMA and lung cancer, a prospective cohort study (Loh, 2011) did not." *Id.* at 25. Dr. Fryzek went on to explain that prospective cohort studies rank higher on the hierarchy of scientific evidence, gave

[25] Discussing Loh, Dkt. 1717-12; DeStefani, Dkt. 1703-8; Goodman, Ex. E.

the reasoning why, and concluded that therefore, "it is likely that some level of recall bias existed in the case-control studies which lead to the increased lung cancer risk finding." *Id.* Dr. Fryzek explained in detail how he properly "accord[ed] appropriate weights to different levels of evidence[.]" *Neurontin*, 2010 WL 559108, at *1 (collecting cases); *see also Johnson & Johnson*, 509 F. Supp. 3d at 194 (finding expert "provide[d] detailed reasons as to why she placed more weight on the cohort studies than the case-control studies" and thus "provided 'good grounds' for her opinions").

However, importantly, Plaintiffs' Motion ignores the methodology Dr. Fryzek actually employed. In ruling out chance, he examined the results from all of the studies as a whole and assessed whether the entire body of scientific evidence on the question was indicative of an association. *See* Tr. at 254:11-16: ("***When you evaluate this literature you can't go through each study and look at the positive aspects of each study***. You have to look at the totality of the literature." (emphasis added)).[26] Indeed, Dr. Fryzek used two forest plots – which are graphs commonly

[26] Dr. Fryzek reiterated this point repeatedly in his deposition. *See, e.g.*, Tr. at 270:8-271:4 ("***You can't just pull out a single study and say that this is statistically significant, so this is an association***. You have to look at the totality of the evidence."), 111:24-112:14, 113:2-113:11, 234:18-236:15 ("Q. And so if they all do not show an association, you do not have a totality of evidence? A. ***You have to look at them all and make an assessment based on all of them***." (emphasis added))

used in epidemiology to display all of the results of scientific evidence on a particular question – in order to assess the totality of the evidence:

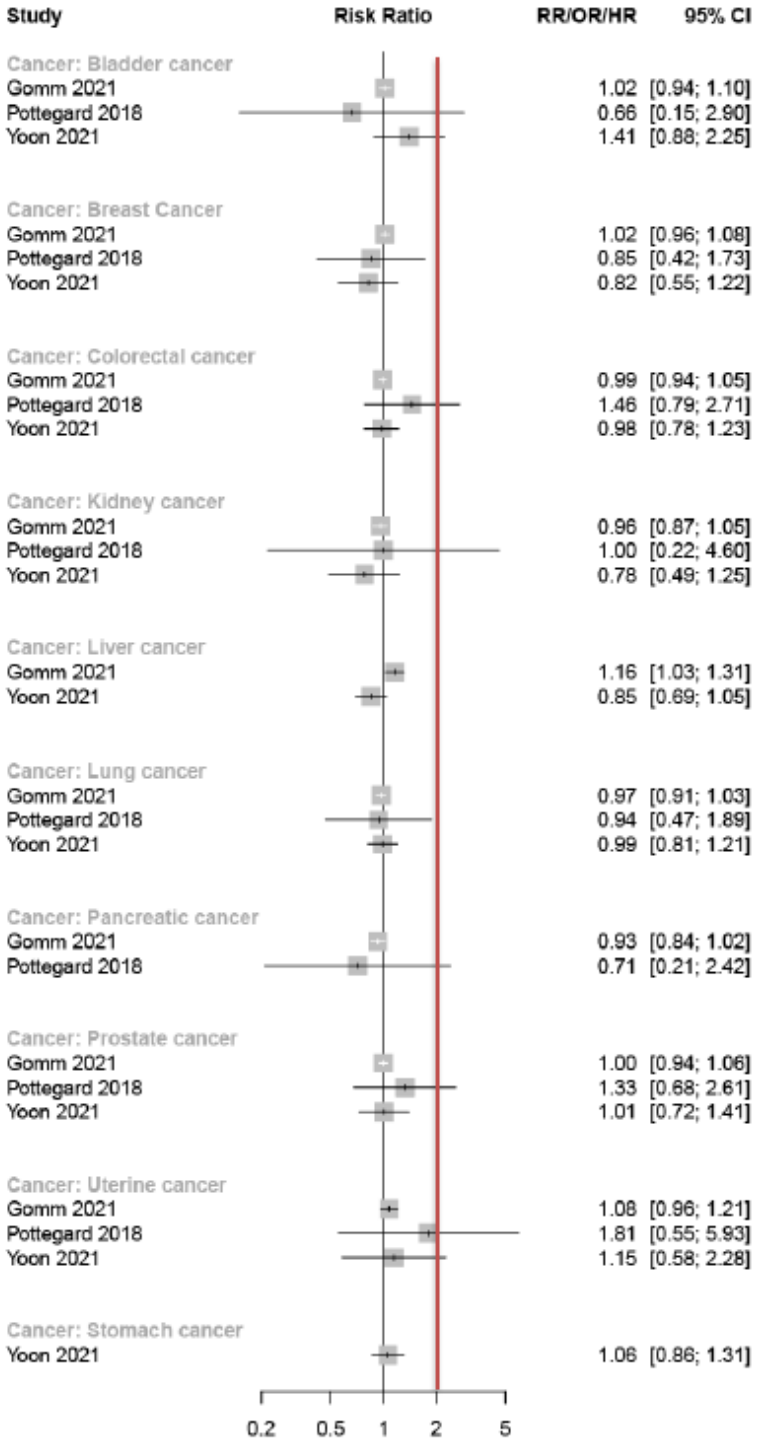

Figure 2. Studies of NDMA-containing medication and risk of cancer

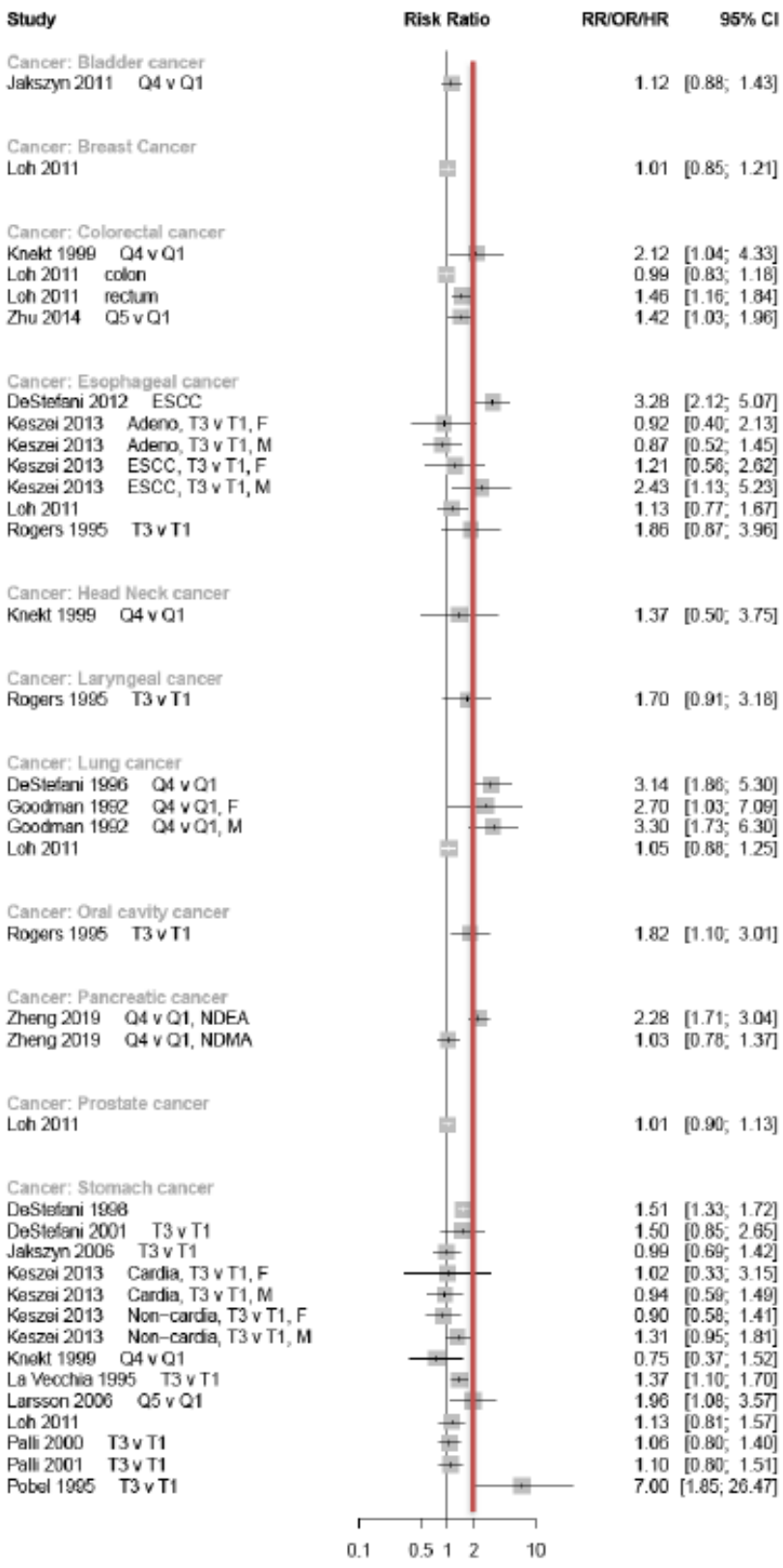

Figure 3. Studies of NDMA or NDEA dietary intake and risk of cancer

Rep. at 14, 20.

Based on his assessment of all of the evidence, Dr. Fryzek concluded that there is simply no relationship between NDMA or NDEA and cancer. *See* Rep. at 18, ¶ 39; *id.* at 34-35, ¶¶ 82-83; *Johnson & Johnson*, 509 F. Supp. 3d at 191 ("It is evident that [the expert] considered the totality of the studies and that his assessment of the studies is based on 'good grounds.'"). Accordingly, Dr. Fryzek's opinions rest on "good grounds" and should not be excluded.

D. Dr. Fryzek Reliably Applied The Bradford Hill Criteria.

Plaintiffs' claim that "Dr. Fryzek's methodology is at odds with Bradford Hill" is both misleading and not factual. Mot. at 13-14. To begin with, Dr. Fryzek did not need to conduct a Bradford Hill analysis because he had not first found that the evidence supported an association between NDMA/NDEA exposure and cancer. *See McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, 2013 WL 3487560, at *15 (W.D. Pa. July 12, 2013) ("If no association between the exposure and the disease is supported by the scientific literature, there is no basis to find a causal relationship exists and the analysis should end there."). Nevertheless, Dr. Fryzek applied the Bradford Hill criteria so as to highlight further the complete lack of any causal association. *See* Rep. at 39-45. With respect to the dose-response factor, Dr. Fryzek's report clearly explains that there is no consistent, demonstrated pattern of a dose-response across the available evidence. *See* Rep. at 40-41.

Plaintiffs raise a non-sequitur in purporting to take issue with Dr. Fryzek's analysis of dose-response in the lung cancer studies, claiming "Dr. Fryzek testified that he discounted the studies that found a positive association because the lowest levels of exposure didn't show an increased risk." Mot. at 13 (citing Tr. at 280:23-281:19). But that is not what Dr. Fryzek's testimony was, nor does it accurately summarize Dr. Fryzek's analysis. As outlined in his report, Dr. Fryzek discounted the marginally statistically significant findings for the highest exposure groups in these two case-control studies because of the limitations of the studies, including bias, multiple uncontrolled risk factors, and failure to see a consistent trend across foods. Rep. at 24-25 ¶¶ 52-54; *see supra* at I.C.2 (discussing lung cancer studies). In assessing the totality of the studies, Dr. Fryzek did not find an association existed.[27]

II. DR. FRYZEK'S EPIDEMIOLOGY OPINIONS "FIT" THE FACTS.

Plaintiffs argue Dr. Fryzek did not have "foundational knowledge" tethered "to facts" because he did not know "the years in which valsartan was potentially contaminated, what ranges of NDMA/NDEA were in valsartan, or even the maximum amount of NDMA/NDEA that has been in valsartan." Mot. at 25. In fact,

[27] In his deposition, Dr. Fryzek explained that "some of the results were inconsistent" for high risk, and "the study design is problematic as well." Tr. at 277:14-279:22. Thus, Plaintiffs claim that "Dr. Fryzek provided no explanation for why he concluded higher levels of NDMA can't cause cancer based solely on lower levels of NDMA not showing evidence of an increase risk of cancer in the same study" conflates dose-response with Dr. Fryzek's proper analysis of the studies as a whole. Mot. at 13.

Dr. Fryzek's opinions regarding whether there is evidence that NDMA or NDEA exposure increases the risk of the cancers alleged by Plaintiffs unquestionably "fit" the facts of this case.

Dr. Fryzek sought to answer the question of whether a causal association exists between NDMA/NDEA exposure and the various cancers alleged by analyzing the existing epidemiological evidence. Accordingly, he properly focused his attention on the published literature when conducting his standard literature review to render his conclusions. *See* Tr. at 124:6-7 ("Our focus was really on the scientific literature. It wasn't on these [internal company] documents."); *id.* at 119:11-13 ("I just reported on what the authors of the studies reported."). Dr. Fryzek had no need to study the levels in the VCDs or the FDA's risk assessment in order to assess the relevant, peer-reviewed literature. *See Adkisson v. Jacobs Eng'g Grp., Inc.*, 2018 WL 3460244, at *14 (E.D. Tenn. July 18, 2018), *aff'd,* 2018 WL 4006782 (E.D. Tenn. Aug. 22, 2018) (finding epidemiologist need not address dose and exposure in order to provide reliable opinion related to general causation).

Indeed, analysis of the issues Plaintiffs raise regarding risk assessment, specific doses, and duration of use are more appropriately addressed by toxicology—which Dr. Fryzek advised Plaintiffs during his deposition.[28] *See* Tr. at 432:23-433:8

[28] For additional information, please refer to Pages 10-11 of Defendants' Brief in Opposition to Plaintiffs' Motion to Preclude Opinions of Defense Expert Janice K. Britt.

("Yeah. I just want you to be mindful, ***this [FDA] risk assessment, it's really a toxicology activity. It's not an epidemiology activity. So it's really outside the scope of what I do.***"(emphasis added)). Plaintiffs cite Dr. Fryzek's deposition testimony out of context when claiming Dr. Fryzek testified that exposure is important. *See* Mot. at 11. Specifically, Plaintiffs attempt to contrast Dr. Fryzek's statement that the ranges of NDMA in the valsartan pills were not "important for [his] review" with the idea that in order for a peer-reviewed article to be accurate, the article must accurately report the population's exposure to the agent. Mot. at 11 (citing Tr. at 106:6-9, 165:13-166:4). But the two concepts are not mutually exclusive, and Plaintiffs' suggestion that they are is misleading and not scientifically supportable.

Dr. Fryzek testified about accurate exposure estimates in the literature when Plaintiffs were questioning him on his critique of Plaintiffs' expert Dr. Etminan for inconsistently faulting studies using dietary questionnaires when it suited him. *See* Rep. at 52 ¶ 128.[29] When asked at his deposition if a study is unreliable if its exposure estimates are unreliable, Dr. Fryzek answered yes and explained that inaccurate exposure estimates impact the results of the studies because the authors are "not measuring what [they] say [they're] measuring." Tr. at 165:1-166:1. However, this statement has nothing to do with assessing the exposure Plaintiffs may have experienced when ingesting the VCDs for a certain duration. Within the literature,

[29] *See* Dr. Etminan's Report, Dkt. 1717-3.

if the study inaccurately reports the population's exposure to an agent, then Dr. Fryzek could not rely on that study to draw any conclusion about whether a causal relationship exists between *the exposure to the agent* and the outcome. Plaintiffs' attempt to take Dr. Fryzek's statement about exposure levels out of context is not a proper basis on which Dr. Fryzek's opinions can be excluded.

Dr. Fryzek's opinions fit the facts of the case because he assessed the question of general causation from the perspective of an epidemiologist based on the relevant, existing literature—not a toxicologist, and not in an attempt to address specific causation. *See supra* at 10-11 n.8 (quoting Ref. Manual at 603 n.161) (emphasizing that analysis of dose response through Bradford Hill "is analytically distinct from determining whether evidence of the dose to which a plaintiff was exposure is required in order to establish specific causation"). His opinions will assist the trier of fact in understanding whether exposure to NDMA or NDEA is capable of increasing the risk of cancer in Plaintiffs, which is critical to the general causation inquiry.

III. PLAINTIFFS' ATTACKS ON DR. FRYZEK'S CREDIBILITY ARE NOT GROUNDS FOR EXCLUSION UNDER RULE 702.

Plaintiffs' attempted challenges to Dr. Fryzek's credibility are not valid legal grounds for the exclusion under Rule 702 of any of his opinions.

1. Plaintiffs' Accusations Are False.

Plaintiffs claim that Dr. Fryzek has never testified at trial, misleadingly citing his deposition testimony. *See* Mot. at 27 ("Dr. Fryzek has never testified at trial, and he should not be allowed to testify at trial in this litigation."). But at his deposition, Dr. Fryzek was only speaking about the ***particular case*** on which he was being questioned. Tr. at 187:11-17.[30] Dr. Fryzek's expert report and Appendix B thereto also demonstrate he has in fact testified two times at trial. Rep. at 3 ("In the last four years, I have testified eleven times at deposition and two times at trial."); *see* Appendix B to Report (identifying that Dr. Fryzek testified in two trials for MDL 2570 on November 2, 2017 and January 31, 2019).

Dr. Fryzek easily rebutted other attempted attacks to his, including regarding his fee. Dr. Fryzek's report lists his hourly rate as $412 per hour, while his fee schedule, Appendix B, to his report, lists $622 per hour. Plaintiffs inaccurately claim that Dr. Fryzek was "not sure" who was being paid the $622 as listed in his fee schedule. Mot. at 8. While at first, Dr. Fryzek did not recall who was paid the $622, his recollection was refreshed with a later exhibit—his actual invoices. Having reviewed his invoice, Dr. Fryzek then testified, "That explains it. That must be what IMS is getting. $622 and then they pay us [EpidStrategies] the $412. . . . [IMS] is a

[30] This line of questioning demonstrates Plaintiffs' counsel's harassing and argumentative behavior toward Dr. Fryzek throughout his deposition. *See* Tr. at 187:17-23 (Plaintiffs' counsel telling Dr. Fryzek that he "hope[d]" Dr. Fryzek would not have testified at a trial because "[he] d[idn't] think [he]'d hold up too well in front of a jury").

firm that finds expert witnesses or hires expert witnesses. This is the first time I've ever worked with them." Tr. at 20:12-19. Plaintiffs omit from their Motion any reference to this clarifying testimony from Dr. Fryzek.

Plaintiffs also complain of a purported discrepancy concerning Dr. Fryzek's academic appointments, but this is pure fabrication. Mot. at 6-9. Dr. Fryzek's CVs list an academic appointment at Vanderbilt University as assistant professor from 2000-2006. Dkt. 1713-9 at 3. During Dr. Fryzek's disposition, Plaintiffs sought to establish that Dr. Fryzek is improperly "attempting to bolster his credentials" by using testimony Dr. Fryzek gave over fifteen years ago. Mot. at 8-9.

Specifically, on February 8, 2005, Dr. Fryzek testified that he was working on grants at Vanderbilt University and that he testified, "[n]ot at this time," in response to the question, "do you teach [at Vanderbilt]?" Mot. at 7-8.[31] But Plaintiffs clearly did not read the entire transcript, in which later Dr. Fryzek testified it was his "understanding that eventually we [at the International Epidemiology Institute] will teach courses at Vanderbilt" (Dkt. 1713-8 at 112:12-13) and "I will start offering coursework at Vanderbilt. . . . It's not a new position. It's part of the duties that we've already [have] . . . It's my understanding that eventually coursework in

[31] Plaintiffs' Motion appears to contain an incorrect cite to Dr. Fryzek's 2005 transcript in citing 26:18-28:24. Mot. at 7-8. Defendants presume the portions to which Plaintiffs refer are 103:10-11 (testifying about working on grants) and 104:12-13 (testifying about teaching). *See* Dkt. 1713-8.

epidemiology will be offered at Vanderbilt and that potentially we will be involved in teaching that." Dkt. 1713-8 at 114:16-115:7.

Dr. Fryzek's 2005 testimony is completely consistent with his present testimony in this case. During his deposition here, Dr. Fryzek testified that his academic appointment at Vanderbilt University was "part of [his] affiliation with the International Epidemiology Institute." Tr. at 25:9-12. Further, he testified his duties as an assistant professor at Vanderbilt entailed him doing "research projects with them, and [he] lectured a couple of times" on "a general seminar about epidemiology." Tr. at 21:6-18. Accordingly, there is clearly no discrepancy in Dr. Fryzek's 2005 and 2021 testimony, nor in his CV. Dr. Fryzek's academic appointment included research and later, between February 2005 and 2006, included teaching a general seminar about epidemiology.

Plaintiffs have also gone so far as to accuse Dr. Fryzek of a crime – and without any evidence. Plaintiffs' counsel bluntly asked Dr. Fryzek if he was currently under ***criminal investigation***. When Dr. Fryzek responded no, Plaintiffs' counsel stated on the record that he hoped he would not "spoil any surprises" before ambushing him with a 243-page report of a Pennsylvania Statewide Investigating Grand Jury. Tr. at 215:22-216:5.

However, Plaintiffs' leap between a grand jury report and accusing Dr. Fryzek of a crime is wholly unsubstantiated. In 2021, a Pennsylvania Grand Jury found that

state officials "did not do enough to properly protect the health, safety and welfare of the thousands of Pennsylvania citizens" from the fracking industry. Dkt. 1713-18 at 10. In the order accepting the report, the Court specifically instructed that "the report may be construed as offering constructive or critical guidance," and "neither the Departments nor its employees [are] being charged with any criminal offenses[.]" Dkt. 1713-18 at 6 ¶ 3 (emphasis added). ***Nothing in the report concerns the actions of Dr. Fryzek.*** Rather, the Pennsylvania Department of Health's Response to the report simply mentions a meta-analysis reviewing existing peer-reviewed literature on the health effects associated with fracking that it published in 2019. Dkt. 1713-18 at 179; *see also id.* at 213-32 (full text of meta-analysis). In that meta-analysis, the authors commented on one article authored by Dr. Fryzek nearly a decade ago[32] and concluded "[t]here is mixed evidence for childhood leukemia owing to conflicting study findings." *See* Dkt. 1713-18 at 219.[33]

In short, Dr. Fryzek has absolutely no connection to any grand jury investigation, and no conclusion can be drawn that somehow Dr. Fryzek's epidemiological methods are unreliable because one of the hundreds of articles he has authored was reviewed in an entirely unrelated meta-analysis.

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[32] *See* Dkt. 1713-19, titled *Childhood Cancer Incidence in Pennsylvania Counties in Relation to Living in Counties With Hydraulic Fracturing Sites*.

[33] The meta-analysis ultimately concluded the same as Dr. Fryzek's article – that "[s]tudies of populations living near ONG operations provide limited evidence . . . of harmful health effects[.]" Dkt. 1713-18 at 213.

2. Plaintiffs' False Narrative Is Not Grounds For Exclusion.

These (false) claims by Plaintiffs regarding Dr. Fryzek "do not suggest [Dr. Fryzek] lack[s] the requisite training, knowledge, and experience to testify as [an] expert[.]" *Viagra & Cialis*, 424 F. Supp. 3d at 790. Plaintiffs' conclusory statement that "Dr. Fryzek's methodology and opinions have been found to be unreliable by numerous sources, and on numerous occasions" is baseless. Mot. at 21. ***Indeed, Plaintiffs do not (and cannot) cite a single opinion from any court limiting or excluding Dr. Fryzek's opinions based on the Rule 702 standards or on any other basis***.

If anything, Plaintiffs' attempts to impugn Dr. Fryzek's credibility are inappropriate as a basis to argue for Dr. Fryzek's exclusion as an expert witness. *See Viagra & Cialis*, 424 F. Supp. 3d at 790 (concluding that attempts to impugn experts, including "pointing out that one is on a 'non-tenure track'" "do not rise to a level that would warrant excluding the experts as unreliable on that basis" and "would properly be explored through cross-examination at trial").

CONCLUSION

For the reasons set forth herein, Defendants respectfully request that the Court deny in its entirety Plaintiffs' Motion to Preclude Opinions of Defense Expert Jon P. Fryzek, MPH, Ph.D.

Dated: December 1, 2021

Respectfully Submitted by the Defense Executive Committee on behalf of all Defendants,

By: */s/ Seth A. Goldberg*
Seth A. Goldberg, Esq.
Liaison Counsel for Defendants

DUANE MORRIS LLP
Seth A. Goldberg, *Liaison Counsel for Defendants*
Jessica Priselac, *Liaison Counsel for Defendants*
Coleen W. Hill
Melissa A. Ruth
30 South 17th Street
Philadelphia, Pennsylvania 19103
Tel.: (215) 979-1000
Fax: (215) 979-1020
SAGoldberg@duanemorris.com
JPriselac@duanemorris.com
CWHill@duanemorris.com

Counsel for Zhejiang Huahai Pharmaceutical Co, Ltd., Huahai U.S., Inc., Prinston Pharmaceutical Inc., and Solco Healthcare US, LLC

GREENBERG TRAURIG, LLP
Lori G. Cohen
Victoria Davis Lockard
Steven M. Harkins
Terminus 200
3333 Piedmont Road, N.E.,
Suite 2500
Atlanta, Georgia 30305
(678) 553-2100
(678) 553-2386 (facsimile)

CohenL@gtlaw.com
LockardV@gtlaw.com
HarkinsS@gtlaw.com

Counsel for Teva Pharmaceuticals USA, Inc., Teva Pharmaceutical Industries Ltd., Actavis Pharma, Inc., and Actavis LLC

PIETRAGALLO GORDON ALFANO BOSICK & RASPANTI, LLP
Clem C. Trischler
Jason M. Reefer
Frank H. Stoy
38th Floor, One Oxford Centre
Pittsburgh, Pennsylvania 15219
Tel: (412) 263-2000
Fax: (412) 263-2001
CCT@PIETRAGALLO.com

Counsel for Mylan Laboratories, Ltd. and Mylan Pharmaceuticals, Inc.

BARNES & THORNBURG LLP
Sarah E. Johnston, *Liaison Counsel for Retailer Defendants*
Kara Kapke
Kristen L. Richer
2029 Century Park East, Suite 300
Los Angeles, CA 90067
Tel: (310) 284-3798
Fax: (310) 284-3894
Sarah.Johnston@btlaw.com
Kara.Kapke@btlaw.com
Kristen.Richer@btlaw.com

Counsel for CVS Pharmacy, Inc.

(incorrectly named as CVS Health Corporation)

ULMER & BERNE LLP
Jeffrey D. Geoppinger, *Liaison Counsel for Wholesaler Defendants*
600 Vine Street, Suite 2800
Cincinnati, OH 45202-2409
Tel.: (513) 698-5038
Fax: (513) 698-5039
jgeoppinger@ulmer.com

Counsel for AmerisourceBergen Corporation

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on December 1, 2021, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system, which will send a notice of electronic filing to all CM/ECF participants in this matter.

/s/ Seth A. Goldberg
Seth A. Goldberg

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